The State of the Pediatric Advisory Committee

(where we have been and where we are going)

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Pediatric Advisory Committee, Tuesday, September 12, 2017

Objectives

- Review involvement of the Pediatric Advisory Committee in reviewing pediatric-focused safety reports over the past (almost) 15 years
- Summarize past (and on-going) efforts to make more effective use of FDA and PAC resources
- Present a proposed plan for future engagement in pediatric pharmacovigilance

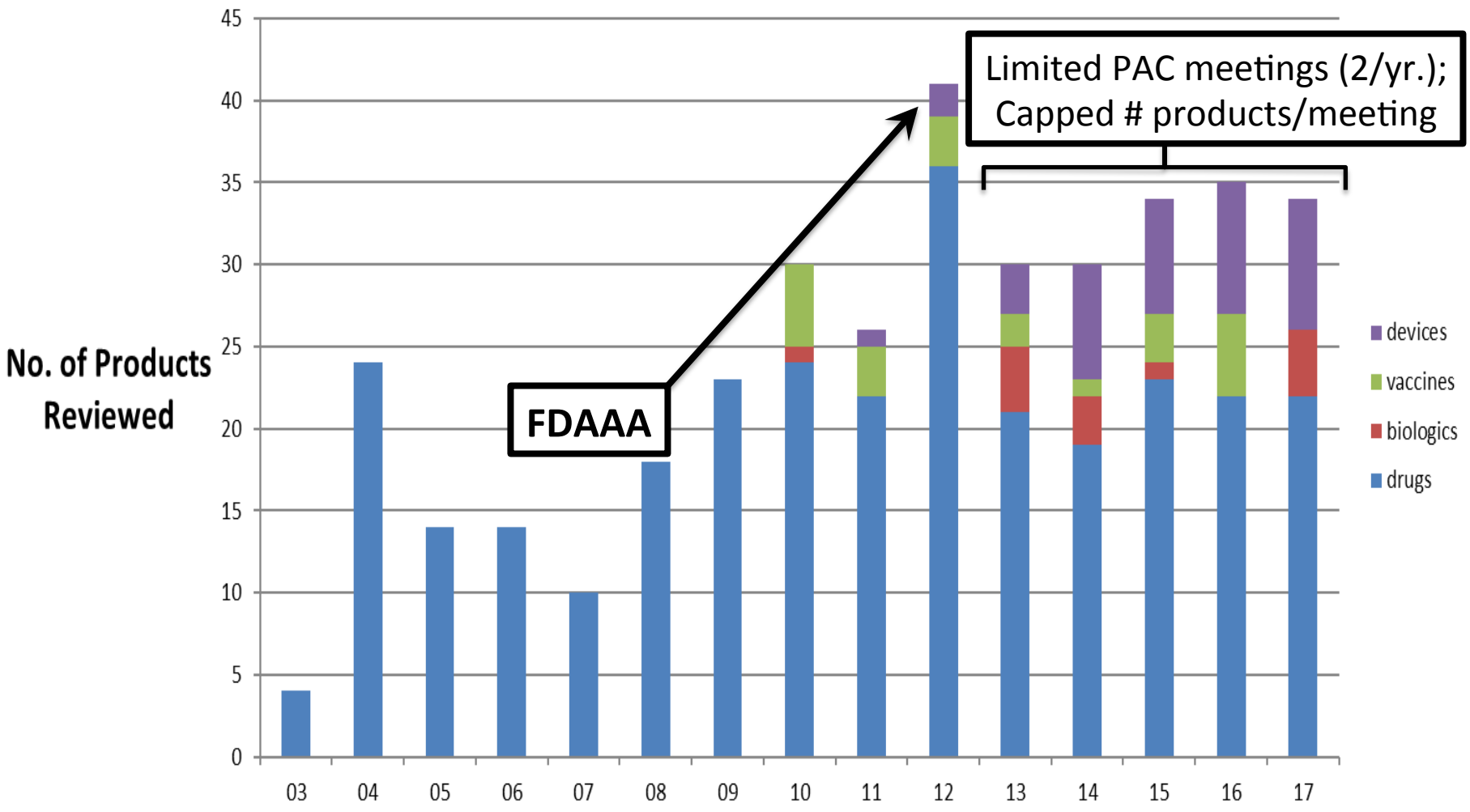
BPCA (2002) and PREA (2003)

- 1997 – *Better Pharmaceuticals for Children Act* enacted as part of the *Food and Drug Administration Modernization and Accountability Act* (FDAMA).
- 2002 - The *Best Pharmaceuticals for Children Act* (BPCA) enacted, which renewed and expanded the 1997 law.
  - Established the FDA Office of Pediatric Therapeutics.
  - During the one year following the date on which a pediatric drug receives market exclusivity, any report of an adverse event must be reviewed by the FDA Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (which first met in 1999).
- 2003 - The *Pediatric Research Equity Act* (PREA) enacted, which codified the 1998 Pediatric Rule.
  - Established the Pediatric Advisory Committee (first meeting – Sept 2004).

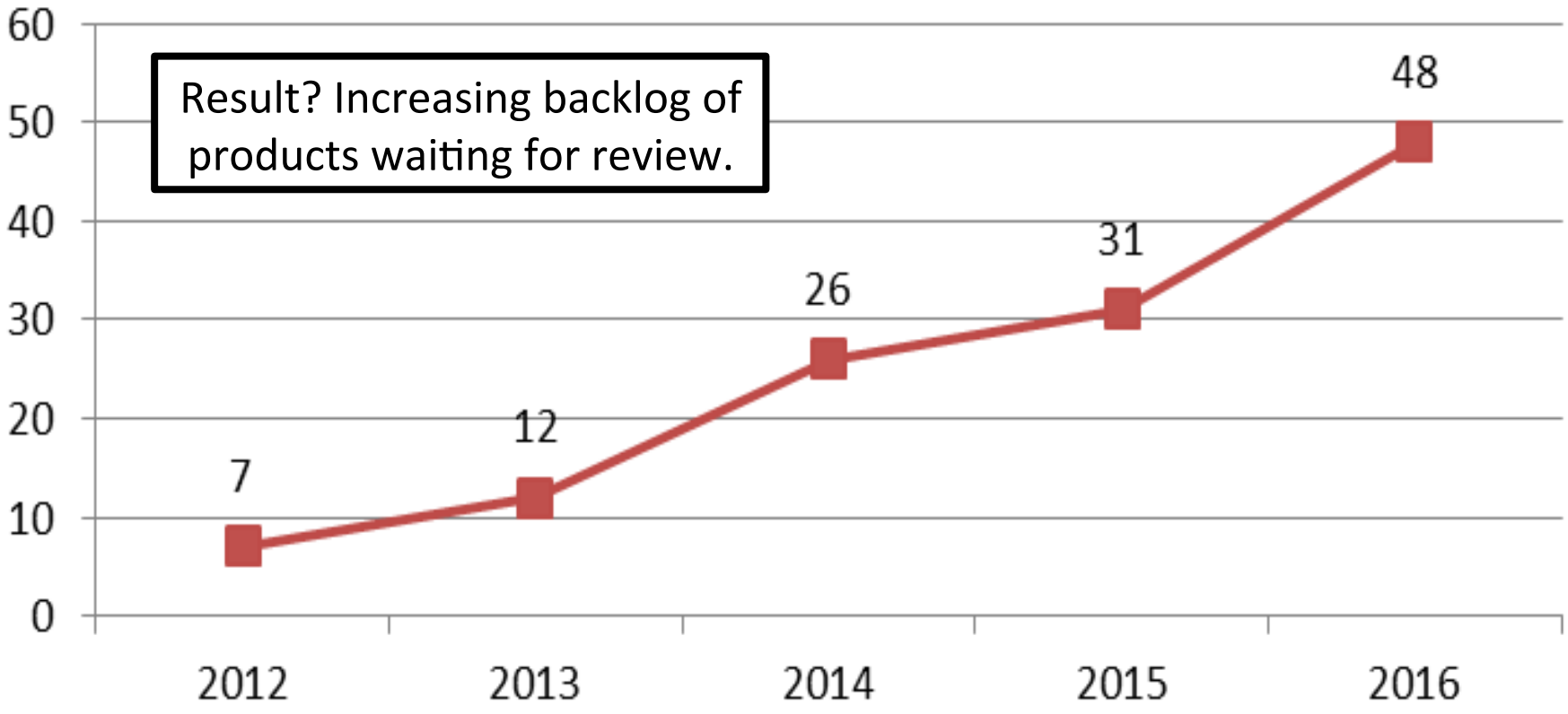
FDAAA (2007)

- The *Food and Drug Administration Amendments Act* (FDAAA) enacted, reauthorizing BPCA and PREA until 2012.
  - Gave FDA explicit authority (under BPCA and PREA) to label a product that has been studied in children, regardless of whether the drug was demonstrated to be safe and effective in pediatrics, including whether the results are inconclusive.
  - Continued (for BPCA) and extended (to PREA; including biologics and vaccines) the adverse event reporting requirement during the one year period following a labeling change (regardless of when a report was received). These reports are reviewed by the PAC.
  - Extended Pediatric Advisory Committee through October 1, 2012.
  - Added PREA, requiring pediatric labeling following studies under PREA and BPCA, and changed the PAC review to follow any pediatric labeling change, increasing the number of reviews that must go to the PAC.

PAC Pediatric Safety Reviews per year, 2003 — 2017 n = 367



CDER Products awaiting PAC Review beyond 21 months of Pediatric Label Change Date



PMDSIA (2007)

- Pediatric Medical Device Safety and Improvement Act of 2007 was incorporated into FDAAA (2007).
- Allowed profit for devices approved under the humanitarian device exemption (HDE) that are specifically designed to meet a pediatric need. The appropriateness of this exemption must be reviewed by the PAC on an annual basis.
- Required adverse event reports for pediatric HDE devices to be referred to the Office of Pediatric Therapeutics. Provided for the periodic review of these reports by the Pediatric Advisory Committee.
- Scheduled to sunset in 2012.

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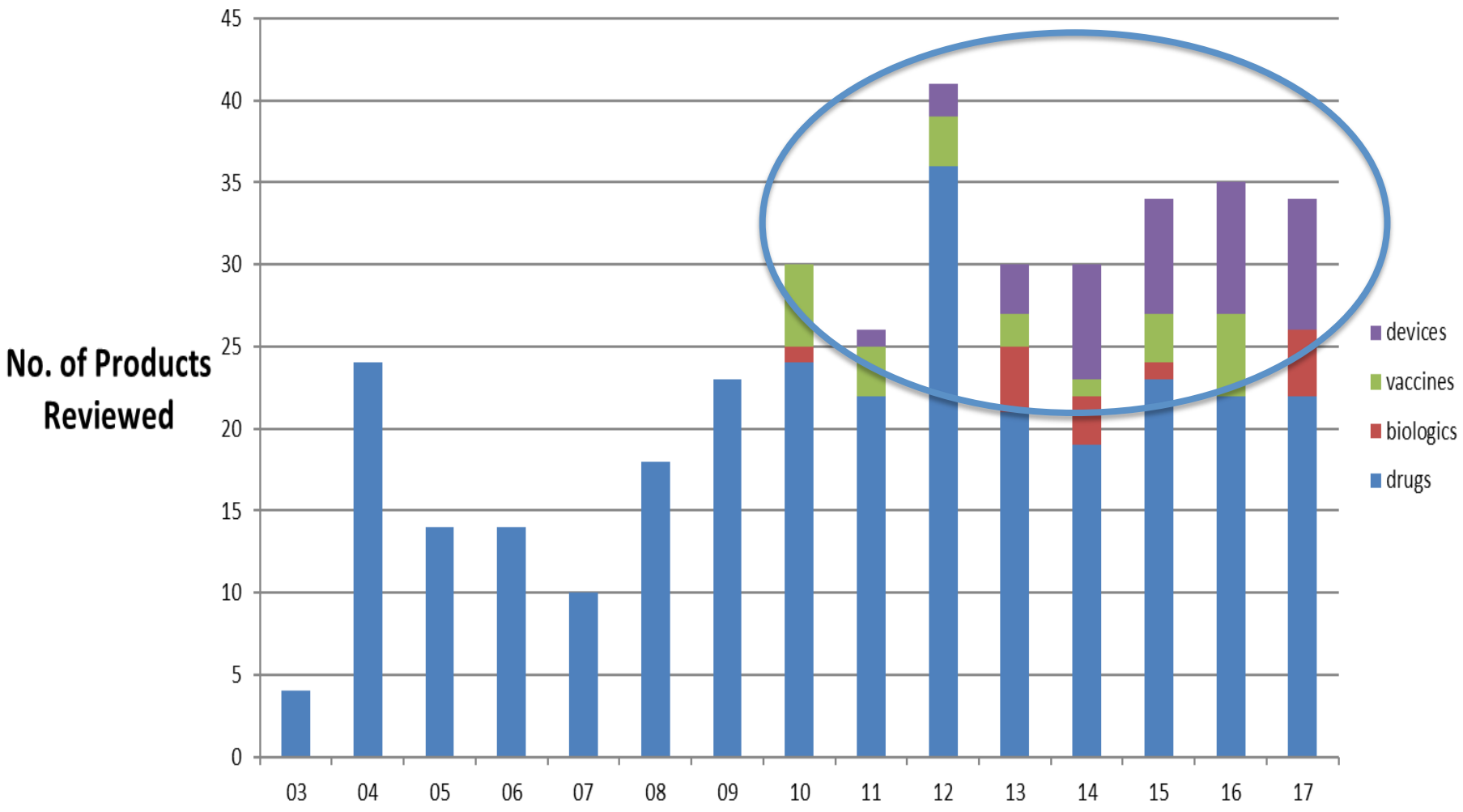
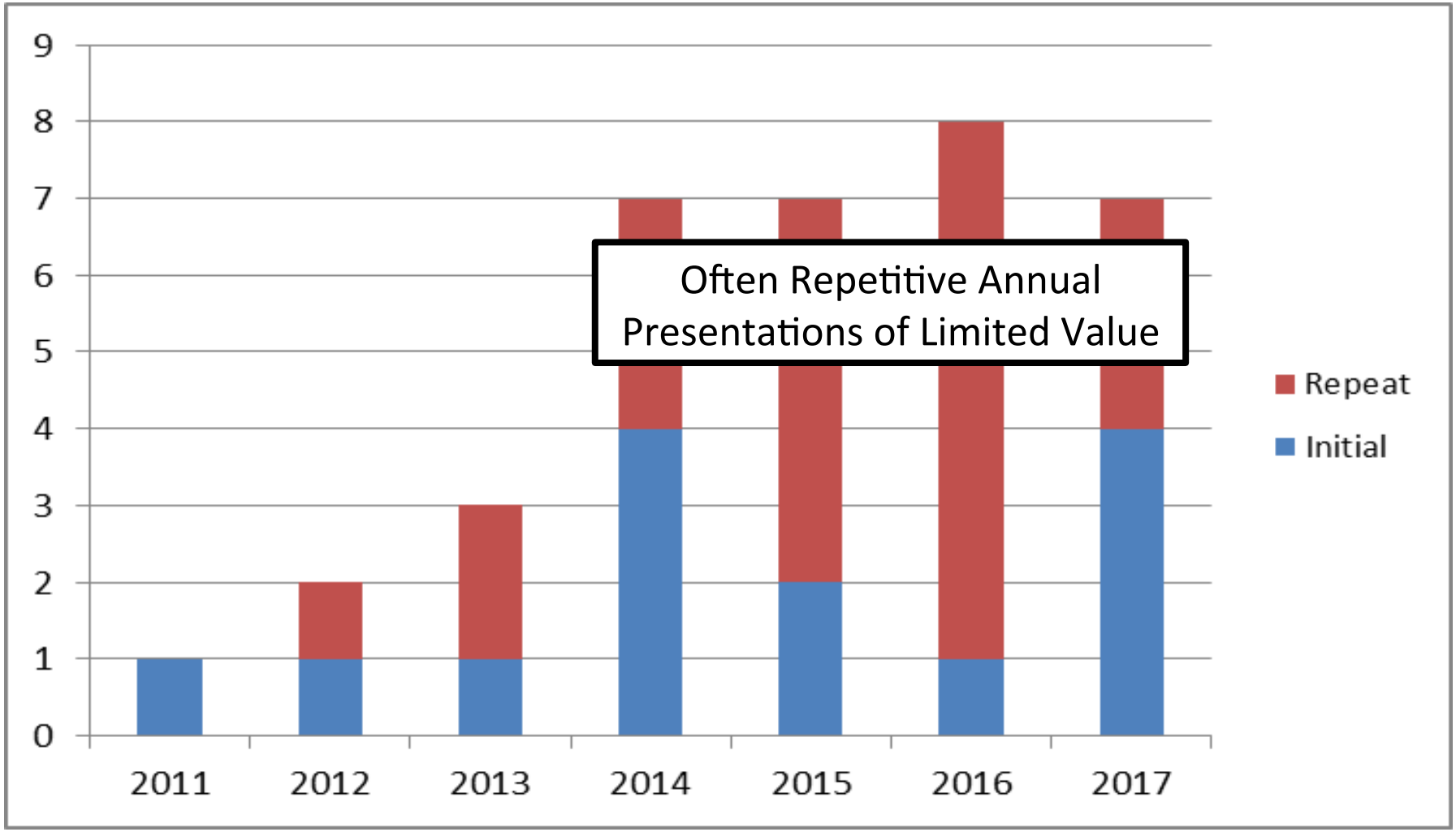


HUD Presentations



FDASIA (2012)

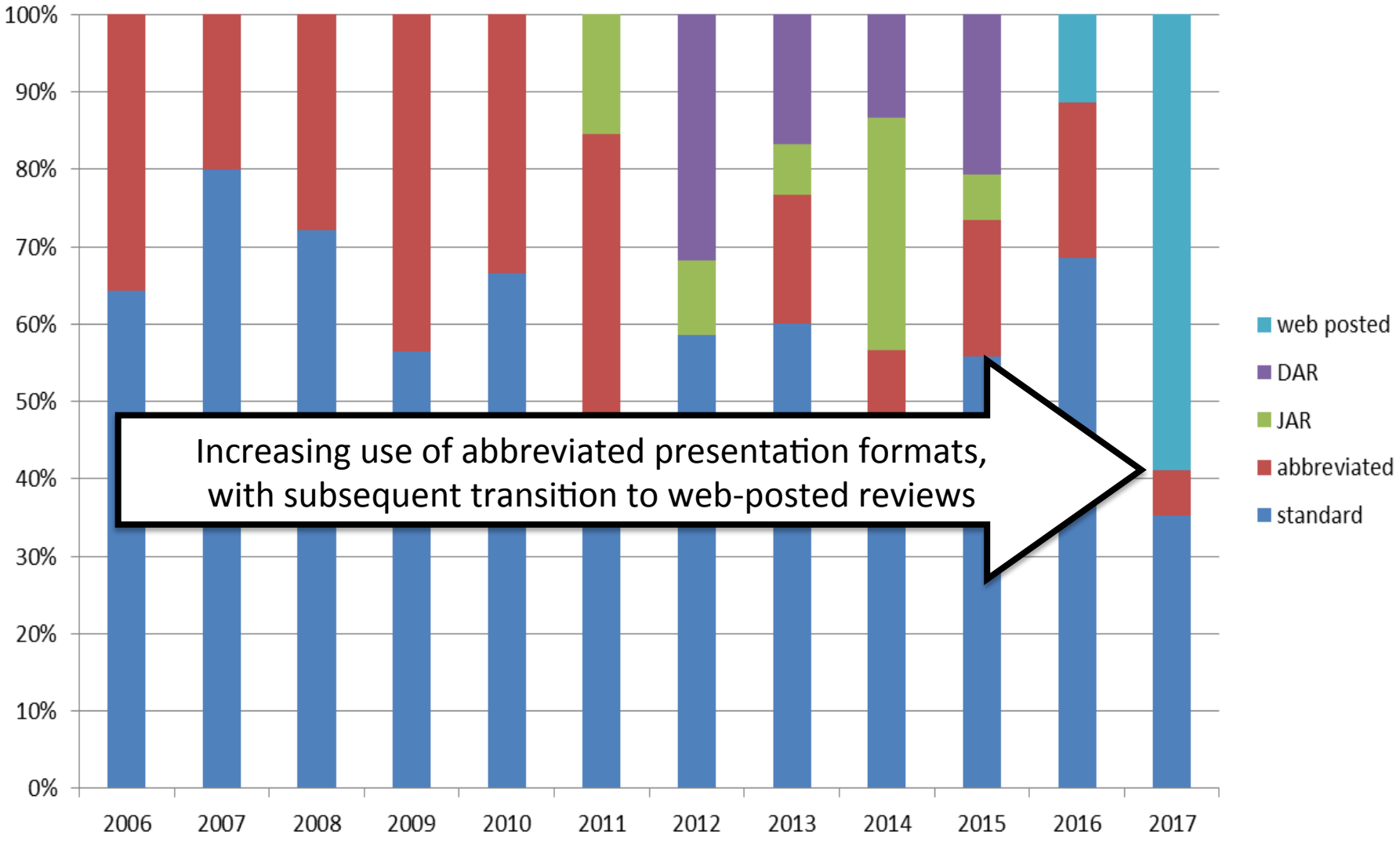
- The *Food and Drug Administration Safety and Innovation Act* (FDASIA) enacted, reauthorizing BPCA and PREA.
  - BPCA, PREA and the PAC were reauthorized permanently (i.e., no sunset).
    - Continued FDA authority (under BPCA and PREA) to label a product studied in children, regardless of whether the drug was demonstrated to be safe and effective in pediatrics, including whether the results are inconclusive.
    - Modified the adverse event reporting requirement from one year to 18 months following a labeling change. These reports are reviewed by the Pediatric Advisory Committee.
  - Gave FDA the authority to grant an extension of the due date for a deferred pediatric study (i.e., "deferral extension").
    - Absent a deferral extension, FDA must issue a non-compliance letter (to which the sponsor must respond), with both letters publicly posted.
  - Reauthorized the HDE profit exemption until 2017.

Better Resource Management

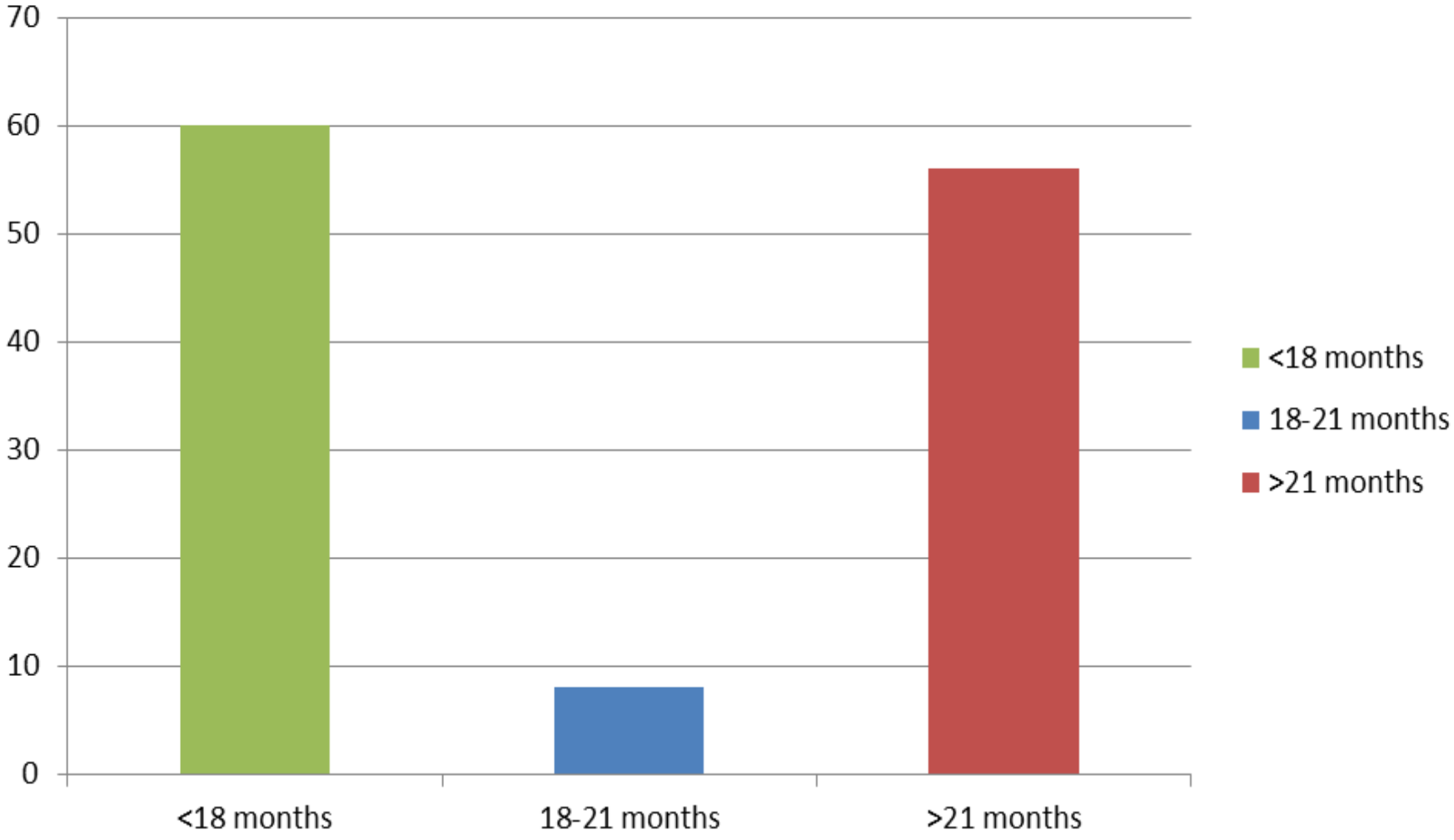
Over the years, we have introduced different approaches to the presentation and review of adverse event reports in order to better use FDA and PAC resources.

- 2006 - introduced "abbreviated" reviews.
- 2010 - introduced "justified abbreviated" reviews.
- 2012 - introduced "designated abbreviated" reviews.
  - Single PAC reviewer (reduce OPT COI review).
- 2016 - introduced web-posted reviews.
  - Initially for CDER products; expanded to CBER in 2017.

PAC Pediatric Safety Reviews by Presentation Format, 2003 — 2017



CDER Products Currently Awaiting PAC Review based on Pediatric Label Date Change



www.fda.gov/pediatrics

FDARA (2017)

- *FDA Reauthorization Act of 2017* enacted on August 18, 2017
  - No changes in the reporting and review requirements for pediatric adverse events following the 18 month period after a labelling change in response to studies conducted under either PREA or BPCA.
  - Extends PREA for products intended for the treatment of an adult cancer that are directed at a molecular target that is substantially relevant to the growth or progression of a pediatric cancer.
    - This change likely will increase the number of products coming to the PAC for a pediatric-focused safety review following pediatric labeling.
  - Requires FDA to inform the PAC of non-compliance letters for deferred pediatric studies and the responses to such letters.
    - The purpose of this requirement is not clear.
  - Reauthorizes the HDE profit exemption until 2022.

PREA Non-Compliance Letters

- Center for Biologics Evaluation and Research (n = 2)
  - https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm448393.htm
- Center for Drug Evaluation and Research (n = 28)
  - https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm343203.htm
- The websites list the sponsor, product, a copy of the non-compliance letter, the sponsor's response (if available), and the status of the PREA requirement (e.g., released, replaced, fulfilled).

HUD PAC Presentation Proposal

- PAC reviews Pediatric Humanitarian Use Devices that have been granted an exemption to sell the device at a profit.
- The statute provides for two aspects of PAC review:
  - Periodic (i.e., as needed) review of HUD adverse event reports; and
  - Annual review to ensure that the product still meets the HDE designation criteria for profit-making pediatric use.
- There is no further specification of the nature, content and frequency of the PAC periodic review of HUD adverse events.
- *Proposal (Spring 2018)*: Annual review for Pediatric HUDs for which no new safety concern is identified will be posted to the FDA website for review and comment. HUDs for which a new safety concern has been identified will be presented as needed.

The Future

- Optimize the use of FDA and PAC resources through appropriate web-posting of drug, device and biologic product reviews.
- Web-post annual device reviews absent a new safety concern that warrants PAC discussion.
- Continue to engage PAC in other advisory committee activities.
- Adjusting internal processes to eliminate the product backlog.
- Explore alternatives to the current time-based labeling-based pediatric-focused safety reviews – considering the option of a public workshop on pediatric pharmacovigilance, followed by PAC discussion of proposed alternative(s).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